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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/036,444	01/07/2002	Alessandro Moretta	1721-44	6065

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/036,444	MORETTA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47 and 60-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47 and 60-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/19/03; 1/7/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 47, and 60-73 are pending and are being acted upon in this Office Action.

2. Applicant's election with traverse of Group 31 Claim 47 (now claims 47 and 60-73) drawn to a method for stimulation of cytotoxicity by NK cells comprising contacting NK cells with antibody or fragment thereof that binds specifically to SEQ ID NO: 2, filed 12/29/03 acknowledged. The traversal is on the grounds that (1) claim 47 is a generic linking claim and SEQ ID NO: 2 is structurally related to SEQ ID NO: 4-7 because SEQ ID NO: 4-7 are fragments of SEQIDNO: 2 (Human NK p30), SEQ ID NO: 4 is the extracellular region of human NK p30, SEQ ID NO: 5 is the transmembrane region of human NK p30, SEQ ID NO: 6 is the cytoplasmic tail of human NK p30 and SEQ IDNO: 7 is a 15 amino acid immunogenic peptide derived from SEQ ID NO: 2 (page 4, lines 5-11 of specification). Upon reconsideration, the prior art search has been extended to include antibody that binds to polypeptide having the amino acid sequence of SEQ ID NO: 4-7 for the claimed method. Therefore, the requirement of Group 31 (now claims 47 and 60-73) and Groups 1-30 and 32-64 is still deemed proper and is therefore made FINAL.

3. Applicant should amend the first line of the specification to reflect the relationship between the instant application and 09/440,514 filed November 15, 1999 stated on the oath.

4. The disclosure is objected to because of the following informalities: (1) "aminoacid" on page 4, line 20 should have been "amino acid". (2) "SEQ ID N°" on page 24, lines 12-27 and Figure 7B-Figure 7C should have been "SEQ ID NO: ".

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 68 and 73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the monoclonal antibody produced by hybridoma I-2576 and hybridomas producing monoclonal antibodies such as AZ20, A76 and Z25 are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification.

If it is not so obtainable or available, a deposit of said hybridoma secreting said monoclonal antibody may satisfy the enablement requirements of 35 U.S.C. 112, first paragraph. See 37 CFR 1.801-1.809.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma I-2576 secreting said antibody have been deposited under the Budapest Treaty and that the hybridoma I-2576 will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or **for the enforceable life of the patent whichever is longer**. See 37 CFR 1.806.

If the deposit has not been made under the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which case the statement need not be verified. See MPEP 1.804 (b).

Amendment of the specification to disclose the date of deposit and the complete name and address of the depository is required.

Applicants are reminded that the current address of the ATCC is as follows and should amend the specification accordingly:

American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

7. Claims 47, and 60-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method for stimulation of cytotoxicity by NK cells comprising contacting said NK cells with an antibody such as polyclonal antibody, monoclonal antibody, humanized antibody and antibody of human origin that specifically binds to a polypeptide comprising SEQ ID NO: 2, or an antibody that binds specifically to a peptide consisting of SEQ ID NO: 4 or SEQ ID NO: 7, **does not** reasonably provide enablement for a method for stimulation of cytotoxicity by NK cells comprising contacting NK cells with any antibody or "antibody binding fragment thereof" of any polyclonal antibody such as AZ20, any monoclonal antibody such as A76 and Z25, antibody produced by hybridoma I-2576, humanized monoclonal antibody, antibody of human origin, which specifically binds to any polypeptide such as a polypeptide "having at least" an amino acid sequence of SEQ ID NO: 2, a polypeptide "having at least" an amino acid sequence of SEQ ID NO: 4 (extracellular region of NK receptor), a polypeptide "having at least" an amino acid sequence of SEQ ID NO: 7, or any antibody or a binding fragment thereof mentioned above which specifically binds to a polypeptide "having at least" an amino acid sequence of SEQ ID NO: 5 (transmembrane region) or any antibody or any binding fragment thereof mentioned above which specifically binds to a polypeptide (intracellular region of SEQ ID NO: 2) "having at least" an amino acid sequence of SEQ ID NO: 6 wherein the antibody or binding fragment thereof is coupled to a label such as a fluorescent label, or attached to a solid support such as paramagnetic microsphere, semi-permeable substrate consisting of an array of hollow fibers and dense particle effective to stimulate their cytotoxicity in vitro. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable

one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method for stimulation of cytotoxicity by NK cells comprising contacting said NK cells with an antibody such as polyclonal antibody AZ20, monoclonal antibody such as A76 and Z25, humanized antibody and antibody of human origin that specifically binds to a NK receptor polypeptide comprising SEQ ID NO: 2, or an antibody that binds specifically to a peptide which is an extracellular domain of said NK receptor consisting of SEQ ID NO: 4 or a peptide consisting of SEQ ID NO: 7 derived from amino acid position 20 to position 33 of SEQ ID NO: 2 (page 31, line 15 of specification). The specification further discloses that the use of AZ20 antibody binding fragment F(ab')2 did not induce triggering of cytolytic activity, indicating that NKp30 stimulation requires efficient crosslinking mediated by the FcγR on target cells (See page 38, line 1-5, in particular).

The specification does not teach how to make and use any antibody or binding fragment thereof mentioned above that binds to any polypeptide "having at least" an amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7 because there is insufficient guidance as to the binding specificity of the antibody for the claimed method since the term "having" expands the polypeptide mentioned above to which the antibody binds to include additional amino acids at either or both ends. The antibody could bind to the undisclosed region of the undisclosed polypeptide, let alone the antibody is effective to stimulate NK cytotoxicity. Further, the polypeptide comprising SEQ ID NO: 2 is a full-length NK receptor that already contains the extracellular region consisting of SEQ ID NO: 4, the transmembrane region consisting of SEQ ID NO: 5, the intracellular region consisting of SEQ ID NO: 6 as well as peptide consisting of SEQ ID NO: 7 that derived from the extracellular region of SEQ ID NO: 2. There is insufficient guidance as to the structure of any polypeptide to which the antibody binds that having at least an amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7, for example. Given the indefinite number of undisclosed polypeptide, it is unpredictable which undisclosed polypeptide is useful for making antibody that is effective for a method of stimulating NK activity.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are

critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

It is well known in the art at the time the invention was made that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Without the specific amino acid residues, it is unpredictable which antibody generated from an undisclosed polypeptide will have the same binding specificity as an antibody generated from the full length polypeptide of SEQ ID NO: 2 or the peptide consisting of SEQ ID NO: 7, in turn, useful for a method of stimulating NK cytolytic activity.

Even if the antibody binds to a polypeptide consisting of SEQ ID NO: 5 or SEQ ID NO: 6, there is insufficient guidance and working example demonstrating that antibody that binds to the transmembrane region of the NK receptor (SEQ ID NO: 5) or the intracellular region of the NK receptor (SEQ IDNO: 6) is effective for stimulation of NK cells cytotoxicity.

Even if the antibody binds to a polypeptide comprising SEQ ID NO: 2, or the peptide consisting of SEQ ID NO: 4 or SEQ ID NO: 7, the specification clearly discloses that the use of antibody binding fragment F(ab')2 did not induce triggering of cytolytic activity, indicating that NKp30 stimulation requires efficient crosslinking mediated by the FcγR on target cells (See page 38, line 1-5, in particular).

With regard to claims 69-70, it is known that labeled antibody such as fluorescent label is for a method of detecting NK cells and not for a method of stimulating NK cell for cytotoxicity by NK cells.

Since the specificity of *any* antibody and structure of the amino acid sequence of any polypeptide to which the antibody binds (epitope) are not enabled, it follows that the method of making and using the antibody for the claimed method of stimulating cytotoxicity of NK cells is not enabled. It also follows that the method of stimulating cytotoxicity of NK cells using any antibody or binding fragment coupled to a label such as fluorescent label, or attached to a solid support such as the ones recited in claim 72 is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 47, and 60-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method for stimulation of cytotoxicity by NK cells comprising contacting NK cells with antibody or binding fragment thereof which specifically binds to any polypeptide such as a polypeptide "having at least an amino acid sequence of SEQ ID NO: 2", a polypeptide "having at least an amino acid sequence of SEQ ID NO: 4", a polypeptide "having at least an amino acid sequence of SEQ ID NO: 5", a polypeptide "having at least an amino acid sequence of SEQ ID NO: 6", and a polypeptide "having at least an amino acid sequence of SEQ ID NO: 7".

The specification discloses only a method for stimulation of cytotoxicity by NK cells comprising contacting said NK cells with an antibody that specifically binds to the NKp30 receptor polypeptide comprising SEQ ID NO: 2, or a peptide which is an extracellular domain of said NK receptor consisting of SEQ ID NO: 4, or a peptide consisting of SEQ ID NO: 7. The specification further discloses antibody that binds to a polypeptide consisting of SEQ ID NO: 5 (transmembrane region) and a polypeptide consisting of SEQ ID NO: 6 (intracellular region) for detection assay.

With the exception of the specific polypeptides mentioned above to which the antibody binds for the claimed method, there is inadequate written description about the structure associated with function of any polypeptide "having at least" an amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7 because the term

having" expands the polypeptide to include additional amino acids at either or both ends so long the polypeptide has at least the claimed amino acid sequences. There is inadequate written description about which undisclosed amino acids to added, let alone to which epitope the antibody binds (binding specificity), in turn, would stimulate NK cytotoxic activity.

Other than the specific polypeptides to which the antibody binds for a method of stimulating NK cytotoxic activity, the other polypeptides are not adequately described. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. Claim 72 is rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "paramagnetic microsphere, semi-permeable substrate consisting of an array of hollow fibers and dense particle" in Claim 72 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the clear support for the said phrase.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 47, 60-63, 69-70, 72 and 73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of a polypeptide "having at least" an amino acid sequence of SEQ ID NO: 2 in claim 47 is ambiguous because SEQ ID NO: 2 is already a full-length NKp30 receptor. Since SEQ ID NO: 2 is a full-length polypeptide, it already contains the extracellular region (SEQ ID NO: 4), the transmembrane region (SEQ ID NO: 5), the intracellular region (SEQ ID NO: 6) as well as the peptide from the extracellular region consisting of SEQ ID NO: 7. It is indefinite and

ambiguous to recite a polypeptide "having at least" an amino acid sequence of SEQ ID NO: 4 (claim 60), a polypeptide "having at least" an amino acid sequence of SEQ ID NO: 5 (claim 61), a polypeptide "having at least" an amino acid sequence of SEQ ID NO: 6 (claim 62), and a polypeptide "having at least" an amino acid sequence of SEQ ID NO: 7 (claim 63). One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention. It is suggested that the phrase "having at least" in claim 47 be substituted for "comprising" since SEQ ID NO: 2 is a full-length polypeptide. It is suggested that the phrase "having at least" in claims 60-63 be replaced with "consisting of" because SEQ ID NO: 4-7 are fragments of SEQ ID NO: 2.

The recitation of "antibody or binding fragment thereof is coupled to a label" in claim 69 has no antecedent basis in base claim 47 because the word "label" is not recited in claim 47. Further, a labeled antibody is for a method of detection and not for a method of stimulation of cytotoxicity by NK cells as disclosed in the specification.

Claim 72 contains the trademark/trade name "MACS". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark is used to identify microbead and, accordingly, the identification/description is indefinite.

The "AZ20, A76 and Z25" in claim 73 is ambiguous and indefinite because "AZ20, A76 and Z25" is merely a laboratory designation which does not clearly define the products for the claimed method, since different laboratories may use the same laboratory designation s to define completely distinct antibodies.

12. The method for stimulation of cytotoxicity by NK cells using the antibody that binds specifically to SEQ ID NO: 2, and SEQ ID NOS: 4-7 are free of prior art.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

15. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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